IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN THE MATTER OF

REINER ET AL.

USSN 09/524,747 ART UNIT 1623

FILED: MARCH 14, 2000 EXAMINER: OWENS, J.

FOR: PHARMACEUTICAL FORMULATIONS BASED ON DICLOFENAC

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Professor Antonio Marzo, do hereby declare and state:

1. I am the Head of the Clinical Pharmacology Department at IPAS SA (Institute for Pharmacokinetic and Analytical Studies) and I am Lecturer of Pharmacokinetics at the Universities of Milan and Parma; my Curriculum Vitae is attached.

2. I am familiar with the U.S. patent application Serial No. 09/524,747 to Reiner et al. (hereinafter "the Reiner application"), first filed in Italy on May 17, 1996, and with the Official Action of January 2, 2003 in which the above-numbered patent application was rejected as allegedly anticipated by European patent application EP466650 (hereinafter "Granger").

3. Copies of references mentioned herein are attached.

4. Abbreviations used herein or in the Reiner application are set forth below:

APR:	Applied Pharma Research, assignee of the Reiner application
AUC:	area under the curve of plasma concentration
BSC:	Biopharmaceutical Classification System
C_{max}:	concentration to the peak
CV%:	coefficient of variation
EC:	enteric coated

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HV(s):	healthy volunteer(s)
I.M.:	intramuscular(ly)
N.R.:	not reported
NSAID(s):	non-steroidal anti-inflammatory drug(s)
RP(s):	rheumatoid patient(s)
t_{max}:	time to peak concentration.

5. The bioavailability of diclofenac has been investigated with various pharmaceutical formulations. A number of researchers have investigated criteria relating to the pharmacokinetics of diclofenac, such as distribution and metabolism, lack of interaction with antacids and the role of gastric pH in the enteral absorption process. However, the problem associated with the variability of the absorption rate and with the so-called "multiple-peak" phenomenon, had not been resolved as of the priority date of the Reiner application (see, for example, Macià et al [1], Henrikson et al [2]; Mendes et al [3]; Crook et al [4]; Willis et al [5]; Willis et al [6]; Riess et al [7]).

6. Data published before 1996 prior to the Italian priority filing date with enteric-coated tablets, sachets, solutions and suspensions of diclofenac are summarized in Table 1. Apart from the publication from Derendorf et al. [8] who report data of I.M. injected diclofenac, the other publications deal with oral administration of diclofenac sodium or potassium or hydroxyethylpyrrolidine salts in solution, or in dispersible tablets or in enteric-coated (EC) tablets. The publications report tests conducting with healthy volunteers, except for Crook et al. [4] which also reports data from rheumatoid patients.

7. Some authors reported data obtained with solutions, describing the following t_{max} values:

Degen et al. [9]	0.3 hr (only 3 subjects were studied)
Maggi et al. [10]	0.62 hr (CV%=35.5), n=12; hydroxyethylpyrrolidine salt
Macià et al. [1]	1.61 hr (range 0.25-2.50 hr) sodium salt in dispersible tablets
Mendes et al. [3]	0.50 hr (range 0.5-2.0 hr) potassium salt in suspension

8. Results published after 1996 include Terhaag et al. [11] who administered diclofenac sodium salt as an oral dispersion and as enteric-coated tablets to 24 subjects. High CV% values were observed in both instances. Thus, the average t_{max} for the suspension was 0.81 hr (range 0.17-4.0 hr), with a CV% of 104.6. For the enteric coated tablets, the t_{max} was 2.01 hr (range 0.50-3.67 hr), and the CV% was 40.9.

9. More recent data on diclofenac potassium salt were published by Marzo et al. [12] and by Reiner et al. [13]. Table 2 summarizes the results of trials testing APR formulations in several comparative bioavailability studies on healthy volunteers against immediate-release reference formulations, already on the market, with particular evidence on time to peak (t_{max}) and related coefficients of variation (CV%). The composition of the tested formulations is reported in Table 3; in particular, the APR formulations used in Trials 1 and 2

correspond to that disclosed in example 12 of the Reiner application, the APR formulations used in Trial 6 correspond to those disclosed in example 13 and the APR formulations used in Trial 3 correspond to those disclosed in example 14. No comparison was carried out over Granger because Granger does not disclose any formulation based on diclofenac.

10. As shown in Table 1, times to peak obtained with formulations according to the present invention (APR) are shorter than those described with tablets, suspensions, dispersions or solutions by other authors.

11. As shown in Table 2, the t_{max} for the APR's formulations always occurred within 0.5hr, irrespective of the nature of the salt (potassium or sodium), or the nature of the formulation (solid or solution), whereas the reference formulations always showed t_{max} later than 0.5hr, and for each trial the CV% for the APR formulation was always lower than that for the reference formulation.

12. Ciba-Geigy have reported a comparative formulation in a pilot study where a t_{max} faster than 0.5hr was observed. However, a very high concentration variability (CV=78%) was observed, in contrast to the APR formulation for which the t_{max} showed a CV% of 0%.

13. The observed lower inter-subject variability (CV%) associated with the APR formulations results in a better reproducibility of the rate of absorption expressed by t_{max} from one subject to another as compared to the reference formulations (Table 2). The CV% was markedly lower with all APR's formulations (between 0% and 60%) than the CV% of the reference formulations (which ranged between 45.2% and 104.7%). However, to my knowledge when the CV of the reference formulation falls within that for the APR formulations, the t_{max} falls outside that for the APR formulations.

14. Only in one case the CV% of the APR formulations was higher than 60%: it is the case of the 50 mg tablet formulation of trial 4 (which exhibited a CV% of 78%). Such a result was however due to a problem in the physical characteristics of a batch and it is not representative; the trial was by the way repeated and resulted in a CV% of 60% (see trial 8).

15. Referring to Figure 1 (showing frequency of occurring t_{max} with APR's test formulation (Test 2 tablet) and Novapirina (reference)), the highest frequency of t_{max} occurring at 0.33 hr (20 min) was detected in more than 80% of the cases with APR's formulation, and only in 50% of the cases with the reference formulation. Furthermore, the t_{max} for the reference formulation occurred up to 2.5 hr, showing high dispersion of the data, while the t_{max} for diclofenac sodium 25 mg tablets by APR occurred not later than 0.5 hr. As shown in Figure 2 the test formulation produced a well evident less data dispersion (bottom graph) than reference formulation (upper graph), both the formulations being administered to the same 24 healthy volunteers.

Figure 1: frequency of occurring tmax with apr's test formulation (test 2 tablet) and novapirina (reference)

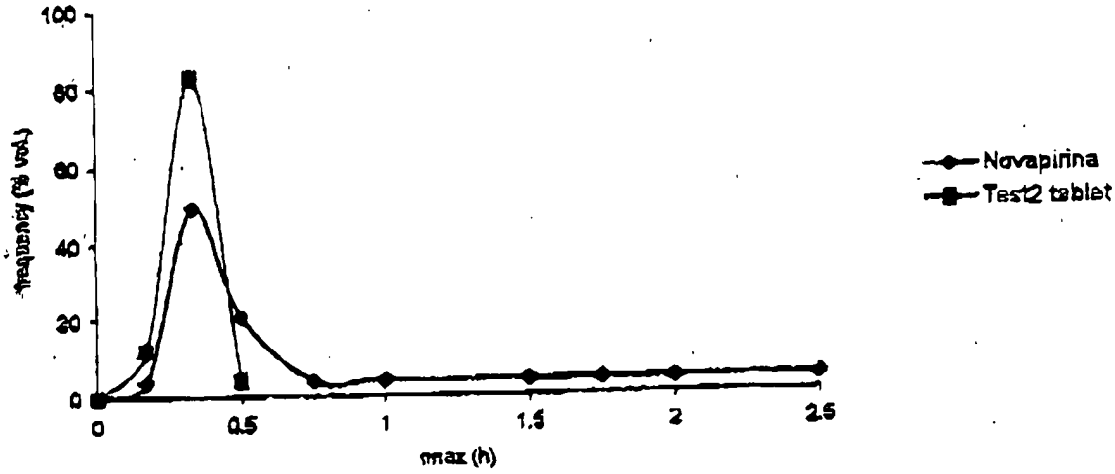
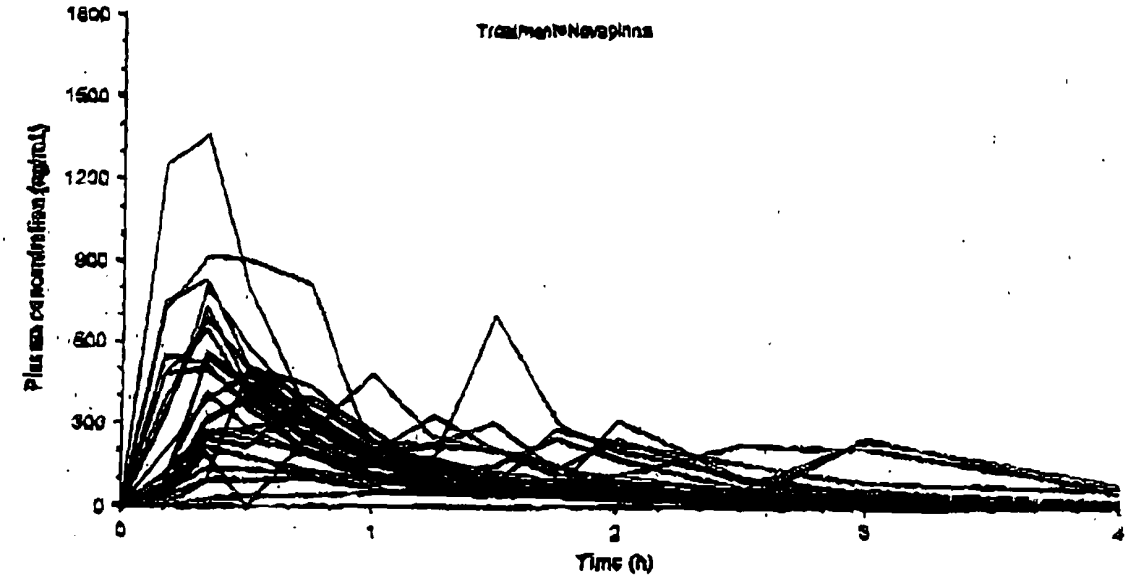
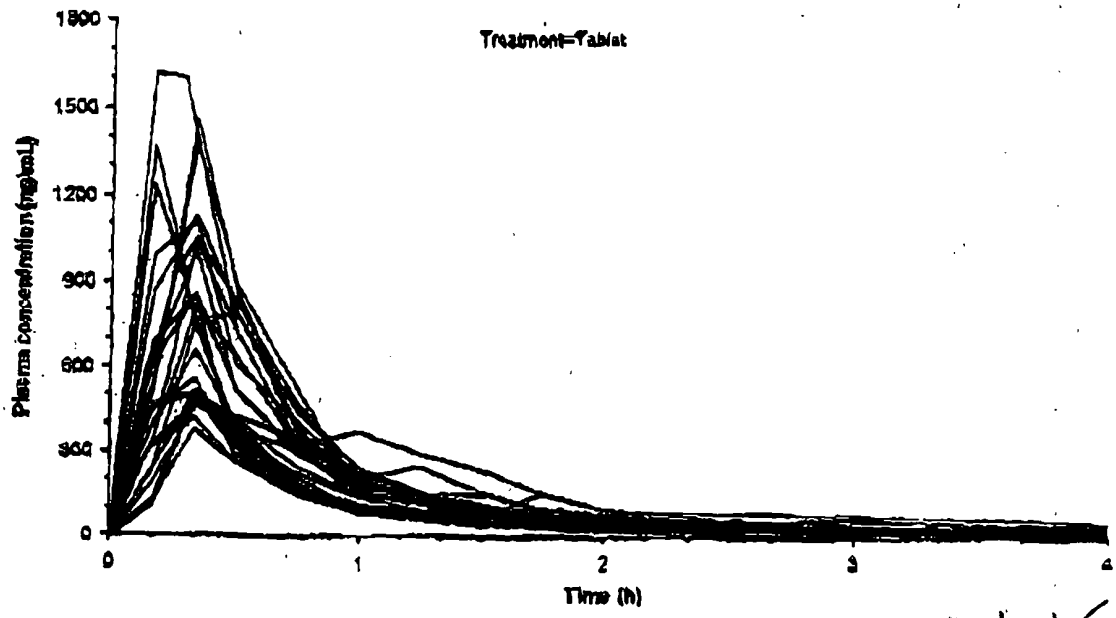


Figure 2: individual overlapping curves obtained on 24 healthy volunteers treated with the test (bottom) and the reference (upper) formulations of diclofenac. Data from trial 7, Table 2.





16. Referring to Granger, this disclosure relates to conferring of a cytoprotective effect or reducing gastrointestinal inflammation in a patient, and describes various non-steroidal anti-inflammatory agents (NSAIDs) which operate systemically through inhibition of the biosynthesis of prostaglandins, particularly PGE_2. At page 2, beginning at line 36, Granger refers to the use of a non-toxic prostaglandin-stimulating metal base or basic salt in the manufacture of a medicament in the treatment of inflammation and states, at page 2, line 48, that the metal can be aluminum, magnesium, sodium, potassium, or bismuth. Granger also states that the metal base or basic salt can be the hydroxide, sulfate, carbonate, bicarbonate, subcarbonate, or trisilicate (page 2, lines 48 and 49). The list of possible NSAIDs which can be used according to Granger comprises at least 34 different drugs (see page 2, lines 10-22). With regard to the metal, this can be aluminum, magnesium, sodium, potassium, or bismuth, and the metal base or basic salt may be the hydroxide, sulphate, carbonate, bicarbonate, subcarbonate or trisilicate. Aluminum hydroxide is the preferred material (see, the Abstract and the working examples).

17. Granger thus discloses formulations consisting of (1) a NSAID selectable from at least 34 different possibilities, (2) a metal selectable from at least five different possibilities and (3) a base or salt selectable from at least six different possibilities. This computes to over 1,000 different possible combinations of components.

18. There is no disclosure in the Granger working examples of the use of diclofenac in combination with an alkali metal bicarbonate and, in particular, with sodium and/or potassium bicarbonate. Granger also provides no disclosure relating to dissolution profiles or hematic levels which can be obtained by administering an oral formulation containing one of the possible disclosed combinations, and affords no disclosure (or suggestion) of improving the absorption of diclofenac with low CV% values.

19. It is important to note that CV% indicates how the T_{max} values are spread over a number of patients. Consequently, the lower the CV% value, the closer are the T_{max} values for the patients, thus making more predictable the time needed to get the maximum therapeutic effect. In the case of an anti-inflammatory drug such as diclofenac, this is very important.

20. In summary, the present method permits the generation of a more rapid and a more uniform, predictive, absorption of the active ingredient, as compared to the compositions of other formulations. This is not, in my view, disclosed (or suggested) by Granger.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issued thereon.

Respectfully submitted,

Antonio Marzo

Name: Antonio Marzo

Title: Professor

Date November 3, 2003

Attachments: CV; Tables 1, 2 and 3; References

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Table 1

Data on diclofenac pharmacokinetics from various authors published or accepted for publication before 1996.

Reference	Dose (mg) and route	Number of subjects	C_{max} (mg/l) range and/or %CV	t_{max} (h) range and/or %CV	Formulation	Notes on bioavailability
Derendorf et al. [8], 1986	75, I.M.	15	2.73 range 1.36-29.7 %CV= 29.7%	0.42 range 0.166-0.664 %CV=41.9	Sodium salt in solution	From this paper after I.M. route a t_{max} of 0.42h longer than values obtained with oral fast-acting APR's formulations is reported.
Henrikson et al. [2], 1982	a) 50, oral b) 100, oral	a) 10 b) 10	a) 0.772 range 0.39-1.100 b) 2.135 range 0.74-2.92	a) N.R. b) N.R.	a) Sodium salt in EC tablets (Voltarol®) b) Sodium salt in EC tablets (Voltarol®)	From Figure 1 of this paper, the two-peak phenomenon seems to has occurred.
Degen et al. [9], 1988	100, oral	3	3.27 range 2.88-3.68	0.33 min=max=0.33h	Sodium salt in solution	Oral solution of diclofenac sodium has achieved the peak at 0.33h in all subjects. However, only three subjects were tested.
Maggi et al. [10], 1990	a) 100, oral b) 100, oral	a) and b) 12 in crossover	a) 2.33 %CV= 21.33 b) 2.10 %CV= 31.4	a) 0.62 %CV= 35.5 b) 2.50 %CV= 26.8	a)Hydroxyethylpyrrolidine salt in sachets for oral solution b) Sodium salt in EC tablets	Oral solution of diclofenac hydroxyethylpyrrolidine allowed the peak to be reached on average at 0.62h (longer than values obtained with oral fast-acting APR's formulations).
Macià et al. [1], 1995	a) 100, oral b) 100, oral	a) and b) 12 in crossover	a) 1.61 range 1.08-2.63 %CV= 33.35 b) 1.88 range 0.60-3.34 %CV= 46.1	a) 1.61 min 0.25, max 2.50 %CV= 50.7 b) 4.59 min 0.74, max 7.80 %CV= 37.5	a) Diclofenac sodium salt in dispersible tablets b) Diclofenac sodium salt in EC tablets	A t_{max} longer than those obtained with oral fast-acting APR's formulations is reported. With dispersible formulation the multiple peak phenomenon was observed in 7 out 12 volunteers.
Mendes et al. [3], 1994	105, oral	18	1.76 %CV= 45.7	0.50 range 0.5-2.0	Diclofenac potassium salt suspension	A t_{max} longer than values obtained with oral fast-acting APR's formulations is reported.

				%CV= N.R.		A high variability in t_{max} values was encountered likely attributable to multiple peak phenomenon.

Table 1 cont.

Reference	Dose (mg) and route	Number of subjects	C_{max} (mg/l) range and/or %CV	t_{max} (h) range and/or %CV	Formulation	Notes on bioavailability
Crook et al. [4], 1981	50, oral	a) 10 HV	a) 1.93 %CV= 32%	a) 2.7 %CV= 40.7	a) Diclofenac sodium EC tablets (Voltarol®)	The authors notice that they have found a high variability in plasma concentrations.
		b) 12 RP	a) 0.99 %CV= 42.4	b) 2.0 %CV= 25.0	b) Diclofenac sodium EC tablets (Voltarol®)	
Willis et al. [5], 1979	50, oral	7	2.0 %CV= 35	2.5 %CV= 44	Diclofenac sodium EC tablets (Voltarol®)	A high variability in plasma concentrations is described, attributable to different values of lag time.
Willis et al. [6], 1981	a) 50, oral fasting	18	a) 1.3 range 753-2022 %CV= 30.3	a) 1.8 range 1.5-2.75 %CV= 27.8	Diclofenac sodium EC tablets (Voltarol®)	A wide inter-individual variation is described, mainly in the non-fasting status.
	b) 50, oral after food		b) 0.78 range 46-1756 %CV= 68.7	b) 5.4 range 2.5-12 %CV= 50.0		
Riess et al. [7], 1981	a) 25, oral	a) 12	a) 0.40 %CV= 37	a) 2.0 range/%CV= N.R.	a) Diclofenac sodium EC tablets	With both 25 and 50 mg the two-peak phenomenon seems to has occurred, with the second peak at 2.5 and 3.0 h with 50 mg and 25 mg, respectively.
	b) 50, oral	b) 6	b) 0.90 %CV= 55	b) 2.0 range/%CV= N.R.	b) Diclofenac sodium EC tablets	

EC= enteric coated; N.R.= not reported; HV= healthy volunteers; RP= rheumatoid patient

Table 2

Main pharmacokinetic parameters of diclofenac APR's formulations and reference formulations obtained in the pharmacokinetic trials

		Trial 1 (n=6)			Trial 2 (n=24)	
		APR, K salt, 50 mg, granulate for sachets	**Form. test by Ciba, K salt, 50 mg sachets**	**Reference, K salt, 50 mg, Voltaren® Rapid tablets**	**APR, K salt, 50 mg, granulate for sachets**	**Reference, K salt, 50 mg, Cataflam® tablets**
C_{max}	**Mean**	1590.72	1438.23	1493.20	2213	1071
	SD	461.60	825.77	1092.89	743	451
	CV%	29.0	57.4	73.20	34	42
	Min	1092.5	487.45	703.23	444	454
	Max	2253.0	2783.84	3515.05	4273	2421
AUC	**Mean**	1206.32	1243.96	1227.92	1362	1214
	SD	364.13	331.27	427.75	358	348
	CV%	30.2	26.6	34.8	26	29
	Min	808.59	844.18	774.06	690	831
	Max	1619.83	1659.37	1867.36	2173	2092
t_{max}	**Mean**	**0.167 (10 min)**	**0.32 h (19.2 min)**	**0.833 h (50 min)**	**0.228 h (13.7 min)**	**0.885 h (53.1 min)**
	SD	0.00	0.25	0.38	0.037	0.860
	CV%	**0.00**	**78.0**	**45.2**	**16**	**97**
	Min	0.167 h (10 min)	0.167 h (10 min)	0.50 h (30 min)	0.167 h (10 min)	0.250 h (15 min)
	Max	0.167 h (10 min)	0.75 h (45 min)	1 h (60 min)	0.267 h (16 min)	4 h (240 min)

Table 2 cont.

		Trial 3 (n=6)			Trial 4 (n=24)			Trial 5 (n=24)	
		APR, K salt, 50 mg tablets	**APR, K salt, 50 mg tablets**	**Reference, K salt, 50 mg, Voltaren® Rapid tablets**	**APR, K salt, 25 mg tablets**	**APR, K salt, 50 mg tablets**	**Reference, K salt, 50 mg, Voltaren® Rapid tablets**	**APR, K salt, drops 50 mg/ml**	**Reference, K salt, 50 mg, Cataflam® tablets**
C_{max}	**Mean**	1873.30	1744.8	1307.0	940.2 (1880.4)*	1766.7	1339.6	1679	1155
	SD	553.80	572.3	558.4	387.0	1020.2	627.5	669	754
	CV%	29.5	32.8	42.7	41.2	57.7	46.8	39.8	65.3
	Min	1228.9	1057.4	581.8	228.5	317.3	336.5	806	186
	Max	2516.5	2468.9	1935.5	1595.4	4516.9	2655.4	3330	3160
AUC	**Mean**	1219	1237	1168	611.81 (1223.63)*	1267.67	1286.43	1392	1198
	SD	246	276	282	144.76	356.46	351.22	423	355
	CV%	20.2	22.3	24.1	23.7	28.1	27.3	30.4	29.6
	Min	874	848	913	380.13	681.89	852.09	845	683
	Max	1615	1668	1642	919.81	2123.22	2185.01	2570	1851
t_{max}	**Mean**	**0.31 h (18.6 min)**	**0.28 h (16.8 min)**	**0.68 h (40.8 min)**	**0.354 h (21.2 min)**	**0.489 h (29.8 min)**	**0.847 h (50.8 min)**	**0.25 h (15 min)**	**0.77 h (46.2 min)**
	SD	0.04	0.07	0.65	0.119	0.366	0.887	0.14	0.73
	CV%	**12.9**	**25.0**	**95.6**	**33.6**	**78.8**	**104.7**	**56.0**	**95.0**
	Min	0.25 h (15 min)	0.17 h (10.2 min)	0.25 h (15 min)	0.250 h (15 min)	0.167 h (10 min)	0.333 h (20 min)	0.08 h (5 min)	0.25 h (15 min)
	Max	0.33 h (19.8 min)	0.33 h (19.8 min)	2.00 h (120 min)	0.750 h (45 min)	1.5 h (90 min)	4 h (240 min)	0.75 h (45 min)	3 h (180 min)

* values normalized to the dose of 50 mg

Table 2 cont.

		Trial 6 (n=24)				Trial 7 (n=24)		
		APR, Na salt, 2 x 12.5 mg tablets	**APR, Na salt, 25 mg tablets**	**Reference, K salt, 25 mg, Cataflam® tablets**	**Reference, diclofenac acid as such, 50 mg, Voltarol®, dispersible tablets***	**APR, Na salt, 25 mg, sachets**	**APR, Na salt, 25 mg, tablets**	**Reference, Na salt, Novapirina® tablets**
C_{max}	**Mean**	847.0	861.3	453.4	351.4	864	863	554
	SD	440.7	395.1	265.49	179.4	300	373	255
	CV%	0.52	0.46	0.59	0.51	34.7	43.2	87
	Min	314.4	221.2	1799.9	108.9	401	382	222
	Max	1700.9	1569.3	992.3	635.2	1720	1620	1360
AUC	**Mean**	570.50	565.59	518.46	506.26	634	632	581
	SD	126.23	159.77	154.54	161.92	152	175	151
	CV%	22	26	30	32	24	27.7	26
	Min	346.13	304.44	322.04	322.71	394	375	355
	Max	859.60	911.34	836.58	858.59	985	974	860
t_{max}	**Mean**	**0.44 h (26.4 min)**	**0.41 h (24.6 min)**	**1.19 h (71.4 min)**	**0.68 h (40.8 min)**	**0.27 h (16.2 min)**	**0.32 h (19.2 min)**	**0.67 h (40.2 min)**
	SD	0.20	0.20	1.03	0.66	0.14	0.07	0.62
	CV%	**46**	**49**	**87**	**96**	**51.8**	**21.9**	**92.5**
	Min	0.17 h (10.2 min)	0.17 h (10.2 min)	0.25 h (15 min)	0.17 h (10.2 min)	0.17 h (10.2 min)	0.17 h (10.2 min)	0.17 h (10.2 min)
	Max	1.0 h (60 min)	1.00 h (60 min)	4.00 h (360 min)	2.00 h (120 min)	0.75 h (45 min)	0.50 h (30 min)	2.50 h (150 min)

* values normalized to the dose of 25 mg

CURRICULUM VITAE

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PERSONAL

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EDUCATION

1958: General Certificate of Education in Lecce

1965: Degree at the School of Industrial Chemistry at the University of Milan

1980: Degree at the School of Pharmacy at the University of Milan

1991: Degree at the School of Pharmaceutical Chemistry and Technology at the University of Milan

PROFESSIONAL EXPERIENCE

Present employment:

Since 1994: Head of Clinical Pharmacology Unit of I.P.A.S. S.A., where pharmacokinetic, bioavailability, bioequivalence, tolerability investigations are carried out in healthy volunteers and target population in compliance with Regulatory Guidelines on Clinical Trials.

Previous employments:

1966 – 1970: Researcher employed by the National Research Council (C.N.R.) at the Departement of Biological Chemistry of Milan University, working on the C.N.R. Endocrinology Project directed by Prof. Vittorio Zambotti.

1970 – 1981: Head of the Biochemistry Laboratory at Simes S.p.A., Milan, where a variety of research projects covering drug metabolism, pharmacokinetics, analytical biochemistry, pharmaceutical technology, quantitative structure-activity relationship and clinical pharmacology were carried out.

1981 – 1985: Head of the Biological Division of B.T.B. Industria Chimica S.p.A., Tribiano, Milan, where research on setting up microanalytical methods, pharmacology, pharmacokinetics and drug metabolism were performed.

1985 – 1989: Head of the Laboratory of Analysis, Pharmacokinetics and Biochemistry at Real s.r.l., Villaguardia, Como, a Company engaged in a business partnership with Sigma-Tau S.p.A., carrying out research on analytical development and pharmacokinetic and biochemical studies on drugs and their metabolites.

1989 – 1993: Head of the Department of Drug Metabolism and Pharmacokinetics of Sigma-Tau S.p.A., Pomezia, Rome, carrying out research on both xenobiotics and endogenous substances for application (IND/NDA) in U.S.A. and Europe.

PROFESSIONAL QUALIFICATIONS

Professional qualifications in the following areas:

Chemical and biochemical analysis, biochemical pharmacology, lipid metabolism, food analysis, enzymology, analytics and microanalytics, pharmacokinetics and drug metabolism, biometrics, chemical quality control, quantitative structure-activity relationships, clinical pharmacology and research and development of new pharmacologically active chemical entities, relations with Regulatory Authorities, both European and U.S.

University teaching

1974 – 1980:	Postgraduate Specialization School in Nutrition Sciences and Dietetics at the Medical School (University of Milan, Italy)
Since 1980:	Postgraduate Specialization School in Pharmacology at the School of Pharmacy (University of Milan, Italy)
1984 - 1985 and since 1996:	School of Pharmacy at the University of Parma

PUBLICATIONS - more than 240

PROFESSIONAL CERTIFICATION
- Pharmacists' Roll
- Biologists' Roll

AFFILIATIONS

- Società Italiana di Farmacocinetica e Bioformaceutica (SIFEB)
- Associazione Farmaceutici dell'Industria (AFI)
- New York Academy of Sciences

LANGUAGES

Italian: Mother language
English: Good written and spoken knowledge
French: Only reading

COURSES AND SCIENTIFIC ACTIVITY DURING THE LAST FIVE YEARS

1998: Invited speaker at the "Fondamenti di farmacocinetica: dalla teoria alla pratica" with the lecture "Ruolo della farmacocinetica nello sviluppo dei farmaci" (Milan, June 16-18)

1998: Invited speaker at the "Fourth European Congress of pharmaceutical sciences", with the lecture "Open questions on bioequivalence: some problems and some solutions" (Milan, September 11-13)

1998: Attendant at the "Third annual Henry Stewart Conference on Understanding bioequivalence and therapeutic equivalence and their documentation for new generic drug applications" (London, September 24-25)

1998: Invited speaker at the "La valutazione del dossier di un farmaco generico", with the lecture "Bioequivalence". This marketing was organised by the Forum Institute of management (Milan, October 22)

1999: Attendant at the "Convenzione europea sui diritti dell'uomo e la biomedicina e problemi etici legati all'analisi genetica applicata all'uomo" (Mendrisio, February 5)

1999: Presentation of 3 scientific papers at the "Fifth Congress of the European Federation of Pharmaceutical Sciences (EUFEPS)" (Jerusalem - Israel, April 25-30)

1999: Invited speaker at the "La ricerca farmaceutica a contratto in Italia: attualità e prospettive" (Milan, October 1)

1999: Attendant to the "Third annual Henry Stewart Conference on Understanding bioequivalence and therapeutic equivalence and their documentation for new generic drug applications" (London, October 26-27)

2000: Organizing Commettee, invited speaker and chearman at the "La farmacocinetica nella ricerca, sviluppo e registrazione dei farmaci" (Milan, February 7-9)

2000: Attendant to the "Incontro tra l'industria farmaceutica Ticinese e l'ufficio intercantonale dei medicamenti" organized by ATICEF (Lugano, Switzerland, October 24, 2000)

2001: Attendant to the meeting "Un utilizzo razionale delle risorse in sanità: medicinali generici" organized by Università degli Studi di Milano (Milan, February 2, 2001)

2001: Organizing Committee, invited speaker and chairman at the meeting "Sinergismo tra biofarmaceutica e farmacocinetica: conclusioni in vitro – in vivo", organized by University of Milan (Milan, February 6, 2001)

2001: Attendant to the "Giornata di studio: metodologia della ricerca clinica in ambito medico" organized by the Ethics Commettee of Canton Ticino (Bellinzona, Switzerland, February 8, 2001)

2001: Attendant to the ronde table "Facciamo largo ai farmaci generici" organized in Milan by Altroconsumo (February 23, 2001)

2001: Invited speaker and chairman at the "Giornata di studio: il farmaco generico in Italia. Sviluppo e prospettiva nell'ottica europea" organized by Gruppo Scientifico Italiano Studi e Ricerche (Milan, March 20, 2001)

2002: Organizing Commettee, invited speaker and chairman at the "Corso di aggiornamento in farmacocinetica: dal drug discovery al complesso problema delle interazioni" organized by Università degli studi di Milano (Milan, February 6-8, 2002)

2002: Attendant to the workshop "Internet: l'e-voluzione delle ricerca clinica" organized in Milan by Hyperphar Research (March 13, 2002)

2002: Attendant to the meeting "Come competere con successo nel mercato dei farmaci generici" organized in Milan by the Istituto di Ricerca Internazionale (May 7, 2002)

2002: Attendant to the "Giornata di studio: il farmaco, perché generico?" organized by AFI (Associazione Farmaceutici Industry), (Novara, September 26, 2002)

2002: Invited speaker and attendant to the Cphl meeting in Paris on October 1-3, 2002

2002: Invited speaker at the "Giornata di studio: l'impatto della circolare del 7 ottobre 2002 sul mercato dei generici e dei principi attivi. Ricalcolo della durata del CCP" organized in Milan (Novembre 27, 2002) by the Gruppo Scientifico Italiano Studi e Ricerche

Date: June 10, 2003

Signature: Alberto Mantovani